Closer Look

MEMORANDUM

MannKind 1Q14 - Awaiting FDA approval decision by July 15; partnership talks and launch preparations ongoing - May 12, 2014

Executive Highlights

- Having completed a successful advisory committee meeting for Afrezza on April 1, MannKind is "eagerly awaiting" the FDA's final approval decision by the recent extended July 15 PDUFA date.
- MannKind is in "intensive" discussions with potential partners.

MannKind shared its 1Q14 financial results today in a call led by CEO Al Mann. The call had just nine minutes of prepared remarks, as management was unable to share anything material on the FDA approval status of Afrezza (PDUFA date: July 15, 2014) or the status of partnership talks - indeed, Mr. Mann called it an "awkward time to speak publicly," as there is so much in limbo right now. Reading between the lines, however, there was clear confidence on both fronts, and management signaled no worries regarding whether Afrezza will be approved or if MannKind will find a partner. Below, we enclose the call's top six highlights, Q&A, and an appendix with a list of potential partners and key questions leaving the April 1 advisory committee.

1. Having completed a successful advisory committee meeting for Afrezza on April 1, MannKind is "eagerly awaiting" the FDA's final approval decision by July 15. In addition to making a final decision on approval, the Agency's "primary task" right now is preparation of the label, the REMS program, and a phase 4 study for children.

2. MannKind is in "intensive" discussions and negotiations with a number of potential partners interested in commercializing Afrezza. A partnership deal could be signed before FDA approval, as management believes "there is enough expectation of approval now."

3. Preparations for commercial launch are underway at MannKind's Danbury, CT facility. The company still expects to launch Afrezza within six months of approval.

4. MannKind has "reserved a booth" at ADA 2014, but "whether to spend the money" and have a formal presence on the floor will depend on the timing of FDA approval.

5. FDA submission of the expanded nine-unit Afrezza cartridge is expected immediately following approval. Submission of the 12-unit cartridge is more likely in late 2015. The call did not mention MannKind's inhalable GLP-1, first discussed at GTC Bio in late April.

6. As of March 31, MannKind had cash and cash equivalents of $35.8 million, reflecting a cash burn of ~$35 million during the quarter. Assuming a cash burn of ~$12 million per month, current financial resources of $85.9 million (cash + loans) will last ~7 months.

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TOP SIX HIGHLIGHTS

1. Having completed a successful advisory committee meeting for Afrezza on April 1, MannKind is "eagerly awaiting" the FDA's final approval decision by July 15. As a reminder, the PDUFA date for Afrezza was extended to July 15 (a "standard three months," emphasized management) to give the FDA more time to fully review the ultra-rapid-acting inhaled insulin. Management repeatedly pointed out that the FDA may not take the full three months, but it's hard to predict when a decision might come. MannKind is "actively working with the Agency to ensure a timely review" - in addition to making a final decision on approval, the Agency's "primary task" right now is preparation of the label, the REMS program, and a phase 4 study for children. Notably, there has been interaction between MannKind and the FDA on a REMS program. Overall, the commentary around the FDA was very positive and suggested that an approval is definitely expected - the uncertainty surrounds the label and REMS.

- **Management recapped the "overwhelmingly positive" April 1 FDA advisory committee for Afrezza.** As a reminder, the FDA EMDAC voted 13-1 in favor of approval of MannKind's inhaled insulin Afrezza for type 1 diabetes, and 14-0 in favor of approval for type 2 diabetes. Overall, we felt the FDA presentations were uniformly negative - the Agency was not convinced of a hypoglycemia benefit, interpreted Afrezza's results as falling short of A1c non-inferiority (in type 1), emphasized high study dropout rates and suboptimal insulin titration, and characterized Afrezza's efficacy in type 2 as "modest" compared to oral agents. However, panelist discussion was, by contrast, patient centered and more focused on the product's convenience. Certainly, the 13-1 and 14-0 votes speak for themselves, and we would imagine a blanket non-approval from the FDA is highly unlikely at this point. That said, much uncertainty remains regarding labeling (e.g., possible pulmonary function screening requirements) and positioning in the diabetes treatment paradigms.
- **Mr. Mann also highlighted the 17 "very strong endorsements" of Afrezza in the panel's open public hearing.** As we noted at the time, this very memorable session included patients who participated in Afrezza trials, several physicians, and leaders of diabetes organizations (Mr. Mann mentioned ADA, AACE, JDRF, Close Concerns, diaTribe, and TCOYD). See our complete report on the advisory committee for more details.

2. MannKind is in "intensive" discussions and negotiations with a number of potential partners interested in commercializing Afrezza. In line with previous calls, no further details were shared, and an announcement is only expected once an agreement is finalized. The call highlighted that a partnership deal could be signed before FDA approval, as "there is enough expectation of approval now." At this point, management said the biggest unanswered questions for a partnership concern Afrezza's label and REMS program. These factors could significantly alter the market success of Afrezza (e.g., approval only in a sub-population, required pulmonary screening, etc.), so this is no small matter for potential partners to consider. MannKind is sharing the status of regulatory discussions with the top potential partners. In Q&A, management confirmed that the plan is to launch in conjunction with a partner, though the company does have contingency plans in place (not further detailed). Said Mr. Mann, "we don't doubt that we're going to get there [i.e., to a partnership]. We're not worried - at least I'm not."

3. Preparations for commercial launch are underway at MannKind's Danbury facility. The company still expects to launch within six months of approval. MannKind is conducting qualification and validation runs, building its operational infrastructure, and working closely with suppliers to ensure demand can be met. In the 4Q12 call, management said that its factory can support up to two million patients, and the expectation was to launch at ~25% capacity. Of course, these numbers are a bit specious as we assume a partner would take on some of the necessary manufacturing and supply-chain investments to scale up production.

4. MannKind has "reserved a booth" at ADA 2014, but "whether to spend the money" and have a formal presence will depend on the timing of FDA approval. If Afrezza is not approved in time (at least a few days/weeks before the meeting's June 13 start), MannKind will not be able to have open conversations about the drug (and thus, a booth would be a waste of money). We would note that MannKind is indeed listed as an exhibitor on the current ADA 2014 floor plan. That said, we would be surprised to see a

full MannKind booth, given the tight timing and the amount of planning that generally goes into exhibit hall booths - in the absence of approval in the next week or two, we'd expect to see (at most) a lounge-only booth with limited signage (e.g., "Seating brought to you by MannKind"). Of course, the dream scenario would include securing FDA approval AND a partnership a couple weeks prior to the meeting, since that would significantly expand marketing potential. At this point, we imagine no formal presence at ADA is likely better than a coming-out party thrown together very last minute. Management did note that ADA 2014 will have a "couple" presentations on Afrezza (we assume focused on the latest phase 3 results in type 1 and type 2 diabetes).

5. On the pipeline side, submission of the expanded nine-unit Afrezza cartridge is expected immediately following FDA approval of the three- and six-unit cartridges. Submission of the 12-unit cartridge is more complicated and would likely occur in late 2015. As a reminder, Afrezza will launch with two cartridge doses: an equivalent to three-units of a rapid-acting analog and an equivalent to six units. The nine-unit version will only require putting more powder in the cartridge, and assuming a six-month FDA review of the supplemental NDA, could be approved almost concurrently with the initial commercial launch of the three- and six-unit cartridges. The 12-unit cartridge "is a little more involved," as MannKind will most likely need to change the concentration of the powder ingredients (adding more insulin to the carrier particle). Said management, "We really need both of those as soon as we can."

- **The call did not mention MannKind's inhalable GLP-1. Early clinical data was shared in late April at the GTC Bio Diabetes Summit.** As opposed to the injectable GLP-1 agonist field, a field that is trending towards longer-acting once-daily and once-weekly candidates, MannKind's inhalable GLP-1 (the native human hormone) is absorbed and out of the system remarkably quickly. A study in healthy volunteers found that GLP-1 levels peaked within five minutes, the resultant insulin secretion peaked within ten minutes (confirmed by C-peptide readings), and glucose lowering peaked at ~30 minutes post-inhalation. The effects were fairly short lasting, due to GLP-1's short plasma half-life. Dr. Andrea Leone-Bay (VP, Pharmaceutical Development, MannKind) emphasized that GLP-1 inhalation produced many of the pharmacological effects of GLP-1 agonist administration (including better fasting and postprandial glycemic control), but with a much lower incidence of nausea and less of an effect on gastric motility, a likely effect of the quick-in, quick-out PK/PD profile. She also said that MannKind is looking into inhalable oxyntomodulin and PYY for obesity.

6. As of March 31, MannKind had cash and cash equivalents of $35.8 million, reflecting a cash burn of ~$35 million during the quarter. Management is "pretty comfortable" that current financial resources are adequate to get to an FDA decision point (i.e., to July 15, unless the PDUFA is extended again). In addition to the $35.8 million in cash on hand, MannKind has access to $30.1 million of available borrowings under the amended loan arrangement with The Mann Group, as well as $20 million per a May 6 loan from Deerfield. The latter is certainly another vote of confidence in MannKind from the highly respected Deerfield. In the 4Q13 call, management stated that available finances would fund operations until at least 3Q14 - assuming a cash burn of ~$12 million per month, MannKind's total current financial resources of $85.9 million should last approximately seven months.

QUESTIONS AND ANSWERS

Q: Let me congratulate you on a very positive Ad Comm - great turnout for you guys. Post Ad Comm, can you give us a sense of the nature of interactions with the FDA? Have you made any progress on the Ad Comm's desire to see longer-term follow-up on DKA and the potential for lung cancer?

A: Please understand that the primary task for the Agency at this point, in addition to making a final decision, is the preparation of the label, the REMS - which is what you're referring to - and also the phase 4 study for children. There has been interaction in between our people and the Agency on a REMS program. It is progressing and is still under consideration by the FDA.

Q: You mentioned in prepared remarks that we could expect to see news "in a few weeks." Can you expand on that?

A: FDA has approximately eight or nine weeks to make their decision. They don't need to take eight or nine weeks - they could do it much sooner than that. Obviously it would be nice to do it sooner so we could have a more open session at ADA in a month. But whether it takes four weeks or eight or nine weeks, I cannot answer.

As for partnership discussions, there are conversations going on now. Those don't have to wait for the NDA to be finalized. I believe that there is enough expectation of approval now - it's just really a question of the details of the label and the REMS program, which are the only issues outstanding at this point. But one never knows what will happen with the regulatory process.

Just to make sure we're all on the same page, Al didn't say "within a few weeks," he said "coming weeks" or "weeks ahead." That's a little more vague than implied by your question.

Q: How are you thinking about cash right now? On the last call, you said you had enough to last through 3Q14.

A: In addition to cash on hand, which could have gotten us close to the revised PDUFA date, but scarily to the edge at that point, we did draw $20 million of additional straight debt from Deerfield - that gives us a little more breathing room. And if we need to, we also have another $30 million under the facility with the Mann Group. We feel pretty comfortable we can get us to a decision point and then see what happens.

Q: Congratulations on the tremendous progress you've made. I understand the sensitivity around partnership discussions. But are you able to share with potential partners some of the back and forth with FDA regarding the label and REMS discussions?

A: We do have sharing sessions between our regulatory people and the regulatory people of the top potential partners. So yes, we are trying to address that in an appropriately collaborative manner.

Q: In the past, you said that from a manufacturing standpoint, you would be able to support commercial launch within six months of approval and partnership. Is that still the case? Has that changed?

A: We are still operating with the expectation that we will be ready to support a commercial launch within six months of approval. Quite honestly, if approval is around July 15, we may even be a little faster than six months because we cannot wait to do our validation runs and get manufacturing ready for commercial operations.

Q: Regarding the supplemental NDA for the 9- and 12-unit cartridges - what are the necessary steps for that?

A: The 9-unit is very actively being worked on right now. The assumption is that immediately upon approval of Afrezza, we would submit a supplemental NDA and hopefully then get a response within six months. That should be almost in conjunction with launch or very shortly upon launch. The 12-unit is a little more involved - we most likely will need to change the concentration of the ingredients on that one, so that is further out in terms of submission. That would probably happen certainly following launch and maybe late 2015.

The difference for the nine-unit is simply putting a little more powder in the cartridge. For the 12-unit, we are adding more insulin onto the carrier particle. How long it will take is hard to say. Hopefully the Agency will not require much for that approval. We really need both of those as soon as we can.

Q: What are the launch plans if you don't sign a partnership agreement this year?

A: We certainly do intend to launch in conjunction with a partner. Do we have contingency plans in place, which will be appropriate for a company like ours? Yes we do. But at this point in time, I would say we feel comfortable regarding the partnership opportunity. We have several different approaches, but we don't doubt that we're going to get there. We're not worried - at least I'm not.

Q: How are you thinking about ADA given less than one month away?

A: Unfortunately, since we don't know when we're going to be approved by the FDA, we are questioning whether we should have a formal operation at ADA. There are going to be a couple of papers about Afrezza, and we reserved a booth there. But whether to spend the money unless we know if we have the approval is the question that's before us now - and we're wondering whether to spend the money on the booth given the circumstances.

Q: If there is a default plan for ADA, do you have one in place?

A: Well, not specifically. We could say that the amount of money we would spend potentially in vain, for a booth, depending on the timing of approval, we could do a lot in terms of other activities in conjunction with ADA. We may even be in a situation where we would have a partnering opportunity there - if we have both a partner and the approval in place at the time. We'll have to a little bit fast on our feet and do the best we can.

I think you can safely assume we will be there. We'll do some presentation at ADA. The question is whether we have a booth on the floor or not. But we'll still be pretty actively involved at ADA.

We would like to have booth, the problem is if we cannot have open discussions, it probably isn't worth spending the money. And we cannot have open discussions without approval. We would need approval days, if not weeks, before the meeting. And we have no guarantee of that.

Q: Just to summarize the comments that you've made on this call. It sounds as if you guys are pretty comfortable not only on the straight up FDA approval, but also in terms of partnering opportunities. If I read in between the lines and the body language - Al, you said you were not worried about much.

A: Well, you don't see our bodies, so I don't know about body language [Laughter]. We are so confident of the significance of this product. There are partners out there that recognize that this is going to be a very, very significant product. We're not really worried - it's just a question of how we're going to launch it. There are several opportunities that we are considering.

Obviously nothing is done until it's done, and we've been confident before. But I can tell you, I'm sitting a few feet from Al, and he doesn't look at all worried to me. [Laughter]

APPENDIX: POTENTIAL PARTNERS

Potential Partner	Motivating Factors	Demotivating Factors
AstraZeneca	-Expanding existing diabetes portfolio beyond incretins	-No experience marketing insulin -Hands full following BMS acquisition, and now, potential Pfizer acquisition
J&J	-Afrezza could be a logical addition in the type 2 diabetes treatment algorithm following Invokana	-No experience marketing insulin -Occupied with market building for Invokana
Lilly	-Deep experience with insulin -No near-term ultra-rapid-acting insulin in pipeline	-Hands full with two basal insulins, dulaglutide, and empagliflozin
Merck	-Januvia's patent expiration/sales slowdown -Experience with first-in-class commercialization (Januvia) -Recent partnership with Samsung Bioepis + glucose responsive insulin	-No experience marketing insulin

	moving into phase 1 signals commitment to insulin	
Novartis	-Strategic complement to Galvus franchise	-No US presence
Novo Nordisk	-Deep experience with insulin -Comfort with exploring alternative delivery technologies (e.g., oral)	-Ultra-rapid-acting insulin aspart is currently in phase 3 -Does not typically partner
Pfizer	-Deal with Merck (ertugliflozin) shows willingness to partner	-Failure of Exubera -Hands full pursuing AZ
Roche	-Following failure of aleglitazar, no late stage novel diabetes drugs	-No experience commercializing insulin
Sanofi	-Deep experience with insulin -No late-stage ultra-rapid-acting insulin	-Focus on U300 glargine, Lyxumia, and LixiLan
Takeda	-Following failure of TAK-875, no late stage novel diabetes drugs -Complement to Nesina franchise	-Will soon be occupied with commercializing Orexigen's Contrave -No experience commercializing insulin

APPENDIX: KEY QUESTIONS LEAVING AFREZZA'S FDA ADVISORY COMMITTEE

The meeting left us with multiple questions - few were answered through the course of the April 1 Advisory Committee. Afrezza has overcome the first regulatory approval hurdle, though the day's discussion seemed to suggest that a lot of the hardest work may lie ahead. We detail many questions that still remain here, in six categories. For more details, see our full report on the advisory committee.

1. COMMERCIALIZATION

- **What is the likelihood of a partnership for MannKind following approval?** A partnership agreement will almost certainly not be signed until after the July 15 PDUFA date, possibly well after, since the label (assuming approval) will represent a huge factor in deal valuation. Additional factors that might be considered are the number and intensity of post-approval trials required (reducing MannKind's resources to participate in a launch), the uncertainty that exists around the size of Afrezza's target population, reimbursement, and the timing of other ultra rapid acting insulins reaching the market.
- **Will payers be convinced that Afrezza is worth reimbursing?** Will they stipulate that people must have already tried and failed a subcutaneous rapid acting insulin?

2. AFREZZA'S LABEL

- **Will the label allow broad use in the general type 1 and type 2 diabetes populations, or will it restrict use to specific subgroups that would benefit most** (as suggested by many panelists)? There aren't any specific data to support segmentation, but there is perceived benefit in people who are non-adherent to injectable insulin and people who have other conditions making it difficult to inject themselves (reduced vision or dexterity) or other conditions that make the rapid onset and offset an attractive option (gastroparesis, proneness to postprandial hypoglycemia).

- **Is there a place for Afrezza in otherwise healthy people with type 1 diabetes?** Dr. Abraham Thomas suggested that Afrezza could be used in between meals to quickly correct for hyperglycemia when a prandial insulin may provide too much stacking - we like to think of this as sort of a "hyperglycemia rescue" dose of insulin, given the ultra-fast-acting profile of Afrezza. Still it remains to be seen how this would work in "real life." For example, Afrezza will first be available in increments of three or six units, meaning that it may not provide enough granularity for type 1 patients that are sensitive to insulin.
- **Will the label include the potential for a hypoglycemia benefit?** Given the FDA's straightforward statement that it is unconvinced of a hypoglycemia benefit and a lack of strong consensus among panelists on this point, we think it is unlikely the FDA will include such a benefit in Afrezza's label. This, of course, could hinder commercialization efforts for Afrezza, since it is one of the agent's most clinically important characteristics (as cited by nearly all of the patient and physician advocates for the drug during the Open Public Hearing).
- **Will MannKind run a trial dedicated to demonstrating a hypoglycemia benefit?** In the clarifying questions, the FDA said it would be "very, very challenging for any sponsor to claim a hypoglycemia benefit for any product." This also was quite surprising. The Agency would want to see a dedicated hypoglycemia study where A1c was matched between the two groups to be able to claim a hypoglycemia benefit. As mentioned above, we think it would be a boon for Afrezza's commercialization to be able to advertise a hypoglycemia benefit and wonder if MannKind or a partner will pursue such a trial.
- **How broad is the pool of people that will be excluded for pulmonary safety risks?** MannKind proposed the exclusion people with COPD and asthma. However, Dr. Stoller suggested excluding people who have ever smoked (~40% of US adults in 2009) rather than just current smokers (18% of US adults today) and people with alpha-1 antitrypsin deficiency (a risk factor for COPD; <1% of American adults). This recommendation was driven by Dr. Stoller's concern over the practicality of expecting providers to actually conduct a spirometry test before prescribing the drug, and every six months thereafter, even if the label calls for it.

3. AFREZZA'S PLACE IN THE TYPE 2 DIABETES TREATMENT PARADIGM

- **Will Afrezza be seen as a replacement for rapid-acting insulin or as an add-on to oral antidiabetic agents?** We would venture to guess that it would not be effective enough to replace rapid-acting insulin for someone who is already on it (an early trial demonstrated inferiority to insulin aspart in type 2 diabetes), and that it would not necessarily offer enough of a convenience/ efficacy benefit to be used in place of any oral agents. We think it will most likely be used in patients already on basal insulin who would otherwise not be willing to intensify to rapid-acting injectable insulin.
- **Will a trial of Afrezza as an add on to a basal insulin be required?** MannKind did not study Afrezza as an add-on to basal insulin, which makes us wonder whether this indication can be claimed in the label.
- **Could Afrezza have the unintended consequence of delaying basal insulin initiation?** Several panelists including Drs. Thomas, Smith, and Wilson questioned if the availability of Afrezza could delay initiation of a basal insulin (e.g., patients who should actually initiate a basal insulin but prefer Afrezza's inhaled administration may opt for Afrezza instead). HCPs could also favor the easier-to-train treatment initiation.

4. POST-MARKETING REQUIREMENTS

- **What structure will a post-marketing surveillance program of cancer and pulmonary risk take?** MannKind recommended a registry of Afrezza users that would be compared against the SEER population (a cancer registry). The FDA indicated that this approach's strength might be that it is the quickest; however, one of its several limitations is that smoking is not measured in the SEER data. Thus, most panelists indicated their preference for a registry with an internal comparator (for

example, comparing patients who remain on Afrezza for a long time vs. patients who started it but stopped right away). The FDA also noted that a randomized clinical trial theoretically could be performed but that it would probably need to enroll over 60,000 people in order to be adequately powered for determining lung cancer risk.

- **Will a post-approval treat-to-target trial be required?** Many panelists expressed a desire for more data on Afrezza's efficacy in both type 1 and type 2 diabetes. The highly respected Dr. Thomas repeatedly called for a treat-to-target trial at least in people with type 2 diabetes regardless of the approval decision. Dr. Thomas indicated that such a trial would help determine its real-life clinical value.
- **Will MannKind be required to further refine its conversion algorithm from subcutaneous insulin units to Afrezza units?** As discussed in more detail in our full report, a major point of contention was Afrezza's dosing and PK/PD. Afrezza appears to have a less-than-linear dose-response relationship, which calls into question whether MannKind's proposed conversion factor is valid (a constant 3.3 multiplier from the subcutaneous insulin dose). At high doses, this conversion factor would underestimate the amount of Afrezza needed and increase risk for DKA (indeed there was an increased rate of DKA for patients on Afrezza in early type 1 studies). Acting Chair Dr. Robert Smith questioned MannKind on whether requiring high doses of Afrezza was a predictor for DKA, and did not seem convinced with the company's data suggesting that it was not. We think Afrezza's dosing may need to be addressed with another PD trial to establish a better subcutaneous insulin-to-Afrezza conversion relationship.
    - Dr. Abraham Thomas also voiced the need for MannKind to provide clarity to patients and HCPs on when a subcutaneous insulin rather than Afrezza ought to be used to avoid DKA. Relatedly, we wonder how useful Afrezza will be for very insulin resistant people who require very high doses of insulin.

5. FDA APPROACHES FOR RISK MANAGEMENT

- **How will the FDA ensure that people with asthma or COPD do not mistakenly receive Afrezza, and how will patients be monitored to ensure that long-term lung function is retained?** MannKind suggested that the label should recommend a spirometry test be performed before Afrezza use, and the FDA indicated that the label will likely call for a spirometry test performed every six months. However, several of the pulmonologists, particularly Dr. Stoller, expressed strong concern about whether these tests will actually be performed and interpreted well. Most PCPs and endocrinologists would need to refer patients to a pulmonologist for the test. We can see the FDA requiring a REMS program where a spirometry has to be performed (similar to the negative pregnancy test required for a woman to receive some highly teratogenic agents like Accutane).
- **Relatedly, how big of a burden would the requirement for pre-prescription and every-six-month spirometry be?** Those caring for people with diabetes most often - PCPs and endocrinologists - are not often equipped with spirometers or able to interpret the results. Thus, most patients would be required to see a pulmonologist every six months for these tests. This may add a barrier for some patients who do not want to go through this hassle (or pay the additional copays).

6. OTHER QUESTIONS

- **Will regulatory researchers and regulatory agencies be able to define a better measure of glycemic control than A1c?** We hope to see increasing use of time in zone, which is now possible with more accurate and reliable CGM.
- **Will researchers and the FDA begin to work on a quality of life measure?** Dr. Stoller and Dr. Wilson pressed that such a measure would be beneficial when evaluating agents (particularly when comparing insulins). Dr. Stoller indicated that this type of metric is already in use in pulmonary medicine.

--by Adam Brown and Kelly Close